AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

Claim 1. (Amended) A method for delivering in vivo a chimeric oligonucleotide into retina cells ~~target cells~~ of a non-human ~~non-animal~~ or human retina ~~eye tissue~~, wherein part of said chimeric oligonucleotide is complementary to part of a sequence of a target gene of said retina ~~target~~ cells comprising a retina ~~an eye~~ disease-causing mutation, wherein the chimeric oligonucleotide is not complementary to the mutation itself, but only to the sequence immediately 5' and 3' of the mutation, ~~and~~ wherein these complementary regions of said chimeric oligonucleotide flank a nucleotide or nucleotides intended to revert the eye disease-causing mutation, and wherein said target gene is selected from the group consisting of cGMP phosphodiesterase, beta-subunit, RP1, opsin and HIF1α gene, said method comprising the steps of:

a) ~~topically applying to or~~ intravitreally injecting into a said ~~the~~ non-human or human ~~eye tissue, or non-animal or human eye tissue adjacent to the non-animal or human eye tissue containing said target cells~~, a composition comprising said chimeric oligonucleotide; and

b) transferring said chimeric oligonucleotide into said retina ~~target~~ cells by iontophoresis.

Claim 2-12 (Canceled)

Claim 13. (Withdrawn) The method of claim 1, wherein said chimeric oligonucleotide is a chimeric oligonucleotide DNA/2'OMeRNA type wherein at least part of the sequence of said oligonucleotide is complementary to a genomic DNA sequence fragment of the murine gene encoding the cGMP-phosphodiesterase β-subunit exhibiting the non-sens C→A mutation in the codon 347 of the cDNA of part of said gene leading to retinitis pigmentosa disease, with the exception of that mutated nucleotide A which is replaced by C in said part of the sequence of said oligonucleotide.

Claim 14. (Withdrawn) The method of claim 13, wherein said chimeric oligonucleotide is selected from the group consisting of:

- the chimeric oligonucleotide DNA/2'OMeRNA type having the sequence SEQ ID No 1; and
- a DNA/2'OMeRNA type chimeric oligonucleotide sequence of which comprising the essential elements of the sequence SEQ ID No. 1 capable of reverting the non-sens C→A mutation in the codon 347 of the cDNA of the murine gene encoding the cGMP-phosphodiesterase β-subunit in animal or human.

Claim 15. (Withdrawn) The method of claim 1, wherein said chimeric oligonucleotide is a chimeric oligonucleotide DNA/2'OMeRNA type wherein at least part of the sequence of said oligonucleotide is complementary to a genomic DNA sequence fragment of the mouse or human gene encoding the transcription factor

HIF1α, with the exception of at least on nucleotide which has been deleted, inserted or substituted in said part of that complementary oligonucleotide, the expressed HIF1α protein coded by the sequence wherein said fragment contains said at least one deleted, inserted or substituted nucleotide being incapable of promoting hypoxia induced neovascularization in human or in mouse.

Claim 16. (Withdrawn) The method of claim 15, wherein said complementary oligonucleotide of the DNA/2'OMeRNA type chimeric oligonucleotide is selected from the group consisting of:

- an oligonucleotide capable of inducing the mutation E142-STOP in the murine or human transcription factor HIF1α; and
- the oligonucleotide having the sequence SEQ ID No. 2 or an oligonucleotide comprising a fragment thereof capable of inducing the same mutation.

Claim 17. (Currently Amended) The method of claim 1, wherein said chimeric oligonucleotide is a chimeric oligonucleotide containing DNA and 2'methoxy RNA wherein at least part of the sequence of said oligonucleotide is complementary to a genomic DNA sequence fragment of said non-human ~~the murine~~ or human target ~~rhodopsin~~ gene, with the exception of at least one nucleotide which has been deleted, inserted or substituted in said part of that complementary oligonucleotide.

Claim 18. (Currently Amended) The method of claim 17, wherein said chimeric oligonucleotide containing DNA and 2'methoxy RNA is selected from the group consisting of:

- an oligonucleotide capable of reverting the mutation K296E or R677-STOP~~66777-STOP~~ in the human rhodopsin protein; and
- the oligonucleotide having the sequence SEQ ID No. 3 or an oligonucleotide comprising a fragment thereof capable of reverting the same mutation K296E.

Claim 19. (Withdrawn) The method of claim 17, wherein said complementary oligonucleotide of the DNA/2'OMeRNA type chimeric oligonucleotide is selected from the group consisting of:

- an oligonucleotide sequence capable of inducing the mutation K296Eor E348-STOP in the murine RP1 protein sequence;
- the oligonucleotide having the sequence SEQ ID No. 5 or an oligonucleotide comprising a fragment thereof capable of reverting the same mutation K296E; and
- the oligonucleotide having the sequence SEQ ID No. 6 or an oligonucleotide comprising a fragment thereof capable of reverting the same mutation E348-STOP.

Claim 20. (Canceled) The method of claim 1 wherein an iontophoresis system used in step b) is a device selected from the group consisting of:

(A) a device comprising a constant current source; applicator and grounding electrodes for emplacement upon patient tissue to provide a current path therethrough for performing iontophoresis upon a portion of said tissue, wherein there is an electrical connection between said current source and said electrodes to thereby produce a voltage differential across said electrodes, an impedance checking circuit coupled to said electrodes and capable of setting predetermined limits of impedance as measured across said electrodes which mark the bounds of safe operation for said device, said impedance checking circuit also capable of signaling the occurrence of impedance values outside these predetermined limits, a safety-shutdown circuit coupled to said impedance checking circuit and capable of responding to said impedance value signal for preventing current flow and voltage differential across said electrodes;

(B) a device comprising a pouch for holding a fluid containing a chemical species, said pouch including flexible and deformable walls adapted to generally conform to surface shapes against which they are placed, at least a portion of which includes a microporous membrane separating the interior of the pouch from the exterior and having openings of about 0.22 microns or less in diameter, said portion being formed to present a generally planar to convex exterior surface, and an electrode carried by said pouch for coupling to an electric potential source, and optionally further comprising a second pouch for holding a fluid containing additional chemical species, said second pouch including flexible and deformable walls adapted to generally conform to

surface shapes against which they are placed, at least a portion of which includes a microporous membrane separating the interior of the second pouch from the exterior and having openings of about 0.22 microns or less in diameter, said portion of said second pouch being formed to present a generally planar to convex exterior surface, a second electrode carried by said second pouch for coupling to an electric potential source, and flexible coupling between the first-mentioned and second pouch;

(C) a device which performs a method of minimizing vesicle formation while applying iontophoretic treatment to a living body, said method including the steps of: conducting direct current through the skin of said body in a first direction from a first electrode to a second electrode on said skin, intermittently reversing the polarity of said electrodes to cause direct current to flow in a second direction opposite said first direction, and controlling the flow of said current in said first and second directions so that the energy applied in said first direction exceeds the energy applied in said second direction by a ratio of between about 2:1 and 7:1;

(D) a device for performing a method of iontophoretic drug delivery wherein an electrochemically active component of either the anode or the cathode of the iontophoresis device is intentionally comprised of a material that effects oxidation/reduction without being consumed to produce a species which interacts with an intentionally selected drug in which a corresponding weak acid/weak base form is selected to be delivered, so that water hydrolysis products are minimized;

(E) a device comprising an aqueous medicament solution including medicament ions and complementary ions, said complementary ions being chloride ions, a first electrode constructed of silver which is capable of reacting with the complementary chloride ion to form silver chloride which is insoluble in the medicament solution, an arrangement capable of placing the first electrode in communication with the aqueous medicament solution, an arrangement capable of placing the aqueous medicament solution in communication with a patient, means for placing a second electrode in communication with a patient at a point on said patient separated from said first electrode, and an arrangement capable of applying an electrical voltage difference between the first and second electrodes such that the medicament ions are transported to the patient, and such that the first electrode reacts with the complementary ions at a voltage below the electrolysis voltage of water;

(F) a device for performing a method comprising the steps of obtaining an ion exchange matrix and a drug comprising medicament ions which are insoluble in an iontophoresis medium and complementary ions, obtaining a first electrode and a second electrode, obtaining an iontophoresis medium, placing the ion exchange matrix and the drug in communication with iontophoresis medium such that the medicament ions are precipitated onto the ion exchange matrix, placing the first electrode in communication with the iontophoresis medium, placing the iontophoresis medium in communication with the patient such that the medium is disposed between the first electrode and the skin of the patient, placing the second electrode in communication

with the skin of the patient at a point distal from the first electrode, and creating an electrical voltage difference between the first and second electrodes, said voltage difference causing the electrolysis reaction of water, the products

of the electrolysis of water acting to solubilize the medicament such that the medicament ions are transported through the skin of the patient, while an approximately constant pH is maintained within the iontophoresis medium;

(G) a device comprising a housing for an electrode, a first chamber which contains an electrolytic solution to permit iontotherapeutic delivery to take place and having present therein ion exchange granules which inhibit increased ionic content through ion generation in the electrode in the first chamber as the iontotherapeutic process takes place, an electrical terminus to contact electrically the electrolytic solution contained in said first chamber, a second chamber for receiving a unit dose of an ionized pharmaceutical, and a permselective membrane separating said first and second chambers, said permselective membrane characterized by having pores with sufficiently low permeability to inhibit substantial passage of said ionized pharmaceutical present in said second chamber into said first chamber, said permselective membrane being substantially free of ion exchange sites;

(H) a device comprising a first electrode for containing a beneficial agent to be delivered and for contacting a body surface of a patient in agent-transmitting relation therewith, a second electrode for contacting the body surface in ion-transmitting relation therewith at a location spaced apart

from the first electrode, first and second electrical power sources, each having a pair of terminals and each producing an electrical potential difference between its said pair of terminals; and a bi-state switch, coupled to said two power sources and said first and second electrode, for selectively switching between: (1) a first state, in which said two power sources are connected in series circuit relation between said first and second electrodes, and (2) a second state, in which said two power sources are connected in parallel circuit relation between said first and second electrode, where switching occurs in response to a change of electrical resistance of the patient's body surface;

(l) a device comprising a medicament-containing disposable patch removably positionable on the skin of a patient for permitting iontophoretic delivery of medicament transcutaneously, a controller including electronic components for electrically controlling said medicament delivery, the patch including a flexible planar patch body having a medicament-containing first surface, an opposed second surface and an extending planar tab for insertable electrical accommodation in said controller, said first surface of said planar patch body being supportable on the skin of said patient, said opposed second surface of said patch body and said controller including co-operative removable fastening arrangement capable of removably fastening said controller to said patch and for maintaining said controller in a fastened condition with respect to said patch with said tab electrically accommodated in said controller;

(J) a device comprising an electrical power source for supplying an electrical current, an electronic controller for controlling the supply of electrical current, a first electrical current distribution element associated with the first side of the electrical power source and a second electrical current distribution element associated with the second side of the electrical power source, a first hydratable matrix element associated with the first electrical current distribution element and a second hydratable matrix element associated with the second current distribution element, first and second hydration means associated, respectively, with the first and second hydratable matrix elements for hydrating said matrix elements, each of said hydration means including a hydration assembly comprising a hydrating liquid, a releasably sealed liquid-storage component comprising a first portion releasably sealed to a strip element to define said releasably sealed liquid-storage component therebetween, and an extending tab member, said extending tab member being continuous with a first end of said strip element, wherein said releasably sealed liquid-storage component contains the hydrating liquid and is disposed with respect to the associated hydratable matrix such that operation of the tab member causes progressive unsealing of the releasable seal that seals the liquid-storage component and causes progressive deposit of the hydrating liquid upon said matrix element;

(K) a device for performing a method comprising the steps of inserting a first electrode into a nasal passage of a subject and applying a second electrode to the subject adjacent the eye or adjacent the ear wherein

said first and second electrodes are each electrically connected to a power source and said target tissue is sandwiched between each of said electrodes to achieve a current path which is of minimal electrical resistance and delivering said composition comprising said chimeric oligonucleotide to said target tissue, wherein the first electrode is a donor electrode and the second electrode is a receptor electrode and wherein the donor electrode is a needle electrode and wherein the donor electrode is a pad for topical administration and wherein the donor electrode includes an electrode body formed from insulating material, a conductor passing through the electrode body and a compartment for storage of the composition comprising said chimeric oligonucleotide located adjacent an outer end of the electrode body;

(L) a device for performing a method comprising applying a transdermal patch to the skin of a living body, causing current to flow through the skin so as to iontophoretically deliver a bisphosphonate compound wherein said compound causes delayed onset of local skin irritation, and reversing the direction of current flow through the skin for a reversal period of long enough duration to reduce effects arising from the delayed onset of local skin irritation caused by the compound;

(M) a device comprising a medicament-dispensing applicator electrode for use with an electrokinetic device to transdermally deliver a medicament to an individual, comprising a substrate having a first surface and a second surface opposite said first surface, said substrate including a medicament-dispensing portion comprising a cell or a plurality of cells forming

an aperture or a plurality of apertures between said first surface and said second surface, said cell or plurality of cells containing the medicament, and a layer of adhesive covering at least a portion of said second surface of said substrate opposite said first surface for releasably attaching said substrate to an electrokinetic device containing an electrical power source for electrokinetically driving said medicament through said first surface and into the individual's skin upon application of an electrical current to effect delivery of said medicament in said cell or plurality of cells to the individual's skin;

(N) a device comprising a reservoir configured to receive the composition comprising said chimeric oligonucleotide and having an internal wall, an external wall, and an end wall bridging the internal wall and the external wall, the internal wall and the external wall being annular and having a free end configured to be applied to an eyeball, said device further comprising at least one active electrode arranged in the reservoir, a passive electrode and a current generator, wherein the at least one active electrode is a surface electrode arranged on an interior surface of the end wall and wherein the internal wall has an outer diameter that is configured to be at least equal to a predetermined diameter, whereby the predetermined diameter represents a diameter of a human cornea; and

(O) a device comprising at least a set of electrodes including an electrode joined to a reservoir that can be charged with the composition comprising said chimeric oligonucleotide and a counter-electrode, an electronic module separably mounted on said set of electrodes to control a

therapeutic electric current flowing between the two electrodes through the reservoir and the skin of a patient applied against said reservoir, said electronic module comprising an arrangement capable of controlling the operation of the device, said device further comprising an electronic key including a memory loaded with a predetermined code, a cradle to temporarily receive said module and an arrangement capable of establishing electrical connections to said module to read this code by reading means present in the module, said control means of said module being responsive to the code of said key to selectively authorize the operation of the device.

Claim 21. (Currently Amended) The method of claim 1 ~~20~~, wherein the iontophoresis system used in step b) is a device comprising a reservoir configured to receive the composition comprising said chimeric oligonucleotide and having an internal wall, an external wall, and an end wall bridging the internal wall and the external wall, the internal wall and the external wall being annular and having a free end configured to be applied to an eyeball, said device further comprising at least one active electrode arranged in the reservoir, a passive electrode and a current generator, wherein the at least one active electrode is a surface electrode arranged on an interior surface of the end wall and wherein the internal wall has an outer diameter that is configured to be at least equal to a predetermined diameter, whereby the predetermined diameter represents a diameter of a human cornea.

Claim 22. (Withdrawn) A method to treat a disease comprising the administration of a chimeric oligonucleotide capable of reverting or inducing a mutation in a target gene of target cells, gene expression of which is associated to that disease, in a human or animal host in need of such treatment, wherein the method used for delivering *in vivo* said chimeric oligonucleotide into said target cells is the method according to claim 1.

Claim 23. (Withdrawn) The method to treat a disease according to claim 22, wherein said disease is an inherited pathology.

Claim 24. (Withdrawn) The method to treat a disease according to claim 22, wherein said disease is an inherited retinopathy.

Claim 25. (Withdrawn) The method to obtain an animal model comprising the administration of a chimeric oligonucleotide capable of reverting or inducing a mutation in a target of target cells of that animal, wherein the method used for delivering *in vivo* said chimeric oligonucleotide into said target cells is the method according to claim 1.

Claim 26. (Withdrawn) A method for the screening of pharmaceutical or cosmetic compounds comprising the use of an animal model, a target gene of target cells of which has been modified by the administration of a chimeric oligonucleotide capable of reverting or inducing a mutation in that target gene, wherein the method

used for delivering *in vivo* said chimeric oligonucleotide into said target cells is the method according to claim 1.

Claim 27. (Withdrawn) A chimeric oligonucleotide DNA/2'OMeRNA type designed with two blocks of 2'O-methyl RNA residues flanking a stretch of DNA, poly(T) hairpin loops and a G-C clamp and wherein part of said DNA/2'OMeRNA sequence is complementary to a genomic DNA sequence of a target gene of said cells with the exception of at least single mismatched nucleotide in the DNA stretch when aligned with the target genomic DNA sequence, characterized in that said at least part of the sequence complementary to that target gene is selected from the group consisting of:

- an oligonucleotide sequence capable of reverting the non-sens C→A mutation in the codon 347 of the cDNA of the murine gene encoding the cGMP-phosphodiesterase β-subunit.

Claim 28. (Withdrawn) The chimeric oligonucleotide DNA/2'OMeRNA type according to claim 27 having the sequence SEQ ID No. 1.

Claim 29. (Withdrawn) A chimeric oligonucleotide DNA/2'OMeRNA type designed with two blocks of 2'O-methyl RNA residues flanking a stretch of DNA, poly(T) hairpin loops and a G-C claim and wherein part of said DNA/2'OMeRNA sequence is complementary to a genomic DNA sequence of a target gene of said cells with the exception of at least single mismatched nucleotide in the DNA stretch

when aligned with the target genomic DNA sequence, characterized in that said at least part of the sequence complementary to that target gene is selected from the group consisting of:

- an oligonucleotide sequence capable of inducing a nonsense mutation STOP in the DNA encoding the murine or human transcription factor HIF1α so that the protein expressed by such a mutated HIF1α gene is not functional;
- an oligonucleotide sequence capable of inducing the mutation E142-STOP in the protein coded by the mouse transcription factor HIF1α, or the corresponding mutation in the human HIF1α protein sequence;
- the oligonucleotide sequence having the sequence SEQ ID No. 2 or an oligonucleotide comprising a fragment thereof capable of inducing the same mutation.

Claim 30. (Currently Amended) A chimeric oligonucleotide containing DNA and 2'methoxy RNA ~~designed with two blocks of 2'O-methyl RNA residues flanking a stretch of DNA, poly(T) hairpin loops and a G-C clamp~~, wherein part of said chimeric oligonucleotide sequence is capable of reverting the mutation K296E in the human opsin protein sequence ~~complementary to part of a sequence of a target gene of said cells comprising an eye disease-causing mutation, wherein the chimeric oligonucleotide is not complementary to the mutation itself, but only to the sequence immediately 5' and 3' of the mutation, and wherein these complementary regions of said chimeric oligonucleotide flank a nucleotide or nucleotides invented to revert eye~~

~~disease-causing mutation,~~ characterized in that said ~~at least~~ part of the sequence ~~complementary to that target gene~~ is selected from the group consisting of:

- ~~an oligonucleotide sequence capable of reverting the mutation K296E in the human opsin protein sequence; and~~
- the oligonucleotide having the sequence SEQ ID No. 3 or an oligonucleotide comprising a fragment thereof capable of reverting the same mutation K296E

Claim 31. (Withdrawn) A chimeric oligonucleotide DNA/2'OMeRNA type designed with two blocks of 2'O-methyl RNA flanking a stretch of DNA, poly(T) hairpin loops and a G-C clamp and wherein part of said DNA/2'OMeRNA sequence is complementary to a genomic DNA sequence of a target gene of said cells with the exception of at least single mismatched nucleotide in the DNA stretch when aligned with the target genomic DNA sequence, characterized in that said at least part of the sequence complementary to that target gene is selected from the group consisting of:

- an oligonucleotide sequence capable of inducing a mutation in the DNA encoding the murine RP1 protein, said mutation being responsible for the expression of a non-functional protein;
- an oligonucleotide sequence capable of inducing the mutation K296Eor E248-STOP in the murine opsin or RP1 protein sequence;

- the oligonucleotide having the sequence SEQ ID No. 5 or an oligonucleotide comprising a fragment thereof capable of reverting the same muation K296E; and

- the oligonucleotide having the sequence SEQ ID No. 6 or an oligonucleotide comprising a fragment thereof capable of reverting the same mutation E348-STOP.

Claim 32. (Withdrawn) A pharmaceutical composition comprising a chimeric oligonucleotide DNA/2OMeRNA type of claim 27.

Claim 33. (Withdrawn) A method to treat a human host having a retinopathy induced y the presence of a mutation in the PR1 gene, comprising contacting in vivo the host PR1 genomic DNA with the chimeric oligonucleotide DNA/2'OMeRNA of claim 30.

Claim 34. (Withdrawn) A method to treat a human or an animal host having ocular neovascularization induced by the expression of the normal transcription factor HIF1α gene, comprising contacting in vivo the host HIF1α genomic DNA with the chimeric oligonucleotide DNA/2'OMeRNA of claim 29.

Claim 35. (Withdrawn) An animal model comprising a mutation in the RP1 gene, mutation which has been induced by the in vivo administration of a chimeric

oligonucleotide wherein said chimeric oligonucleotide is a chimeric oligonucleotide according to claim 31.

Claim 36. (Withdrawn) Use of an animal model according to claim 35 for the screening of pharmaceutical compounds capable of treating human or animal retinopathies.

Claim 37. (Withdrawn) A pharmaceutical composition comprising a chimeric oligonucleotide DNA/2OMeRNA type of claim 28.

Claim 38. (Withdrawn) A pharmaceutical composition comprising a chimeric oligonucleotide DNA/2OMeRNA type of claim 29.

Claim 39. (Previously Presented) A pharmaceutical composition comprising a chimeric oligonucleotide containing DNA and 2'methoxy RNA of claim 30.